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WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
HOLT, ANDRIAE M	

ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,454	EYJOLFSSON, RENIR	
	Examiner	Art Unit	
	Andriae M. Holt	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed December 8, 2008. Claims 1-12 and 15-16 are pending in the application. Claims 13-14 were cancelled in a previous office action.

The rejections of the previous Office Action **are maintained**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris et al 4,743,450 in view of Daniel et al. WO99/62560.

The compound of formula 1 is the basic structure for an ACE Inhibitor, which is well known in the art, including the weight percentage ranges. Harris teaches the combination of formula 1, (col. 2, formula I, line 15-20), component b, an alkali or alkaline earth metal carbonate to be used as a stabilizer (col. 1, line 60 and col. 3, lines30-34), and saccharide compound used in the mixture (col. 1, line 61), the formulation by which the industry standard ace inhibitor, Accupril (Pfizer, Inc. and Warner Lambert, US Patent 4,743,450) is produced. Harris et al. does not specifically

teach or make provision that the formulation does not contain a substantial amount of a saccharide compound. However, as defined in the specification of the instant application "a substantial amount of a saccharide compound" is any amount that would generally be considered to have a stabilizing effect on the active compound, such as more than about 10 wt % and more preferably including an amount which is more than about 5 wt% (page 3, lines 18-22). The wt % ranges for the provision of the instant invention are within the specification of Harris et al, 1% to about 90%, preferably about 10% to about 80% (col. 3, lines 56-58).

Harris et al. does not teach an insoluble alkaline-earth metal salt of hydrogen phosphate. Daniel et al., however, does teach a hydrolysis-minimizing agent suitable to retard hydrolysis in combination with an ACE inhibitor, which is susceptible to cyclization, hydrolysis, and/or discoloration, and (b) an effective amount of magnesium oxide suitable to retard cyclization, hydrolysis, and/or discoloration. Daniel et al. specifically sites as an example, dicalcium phosphate, a calcium mono hydrogen phosphate, that is insoluble in water (page 3, lines 20- 24).

It would have been obvious to one skilled in the art at the time of the invention to have been motivated to combine the practices of the formulations of Harris et al. and Daniel et al. That is substituting the hydrolysis minimizing- agents, saccharides with an insoluble alkaline-earth metal salt of hydrogen phosphate. Each essentially performs the same function of retarding hydrolysis of an ACE inhibitor that is susceptible to hydrolysis. It has been discovered that useful, stable formulations can be produced

using excipients comprising basic compounds as evidenced by the formulations produced by Harris et al. and Daniel et al. Each formulation using the basic compounds has been proven to be effective and efficacious ACE Inhibitors in reducing hypertension in patient populations. The use of these compounds in combination has proven to have greater storage stability and more suitable for use in drug combinations (Harris et al. col. 1 lines 36-38). The active ingredients or drugs contained therein are virtually preserved from cyclization and hydrolysis. In addition, the discoloration, which sometimes occurs when ACE inhibitors of this class are formulated and allowed to stand for significant periods of time, is minimized or eliminated completely (Harris et al col. 1, lines 27-33). It is well known in the art that it would be advantageous to manufacture stable ACE Inhibitor agents using basic compounds because these compounds are more cost effective to make or purchase.

In reference to claim 2, Harris et al, teaches the use of an alkaline stabilizer included in Group I and II of the periodic table combined with an anionic salt, magnesium, calcium and sodium are the preferred earth metals. Magnesium is most preferred. Carbonates are the preferred anionic salt (col. 3, lines 30-39). Harris et al. teaches claim 3 that the amount of alkaline earth metal carbonate is at least equal to the amount of the active compound of formula I, as evidenced by comparing example 1 of the instant invention (Specification, page 5, lines 5-15) and example 1 of Harris et al. (col. 4, lines 56-67).

Claims 4 and 10 are taught by both references. Daniels et al., page 6, line 15, teaches enalapril and quinapril or, their corresponding free acids or pharmaceutically acceptable acid addition or base salts thereof. Harris et al., col. 2 lines 32-34, teaches enalapril and quinapril, their free acids or pharmaceutically acceptable acid addition or base salt thereof. These ace inhibitors are well known in the art. They each have very similar properties, including the structure of Formula 1 in Harris et al. (col. 2, line 15, formula 1). The weight ranges in claim 5 are taught by Harris et al. (col. 2, lines 38-40). The total weight ranges for the total composition is 1% to about 70 %, preferably from about 1% to about 25 %.The weight ranges of claims 6 and 7 of the alkali or alkaline earth metal carbonate are taught by Harris et al. (col. 3, lines 40-44) as the quantity of stabilizer to be used will lie between about 1% and 90%, preferably about 10 % to about 80 %, encompassing ranges specified in the claims of the instant invention.

As per claims 8 and 9, Daniels et al., teaches the use of hydrolysis minimizing agents, including dicalcium phosphate, which is a calcium mono hydrogen phosphate, which is insoluble in water. The quantity of the hydrolysis- minimizing agent should be about 10% to about 95% preferably about 50% to about 95%, and most preferably 70% to about 90% (page 9, lines 5-17).

The suitable categories of drugs that can be combined in the embodiment of claim 11 of the instant invention are well known and well used in the art as categories that can be combined with ACE inhibitors, particularly quinapril, to provide an effective and efficacious anti-hypertensive agent with additive effects. Harris et al. and Daniel et

al. teach claim 11 (Harris et al., col. 2, lines 60-68 and col. 3, lines 1-10; Daniel et al., page 7, lines 11-26).

Claims 12 and 15-16 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Harris et al. (US 4,743,450) in view of Daniel et al. (WO 99/62560).

Applicant's Invention

Applicant claims a pharmaceutical formulation of compound a) an ACE inhibitor, b) an alkali or alkaline earth metal carbonate, c) an insoluble alkaline-earth metal salt of hydrogen phosphate, and d) less than 5 wt % of a saccharide compound. Claims 15-16 define the amount of the saccharide compound in the formulation as less than 2 wt% or do not contain a saccharide.

Determination of the scope of the content of the prior art (MPEP 2141.01)

The teachings of Harris et al. are incorporated herein by reference and are therefore applied in the instant rejection as discussed hereinabove. Harris et al. teach the quantity of the saccharide present will be from about 5% to about 90%, preferably about 10% to about 80% (col. 3, lines 56-58) (claim 13, less than 10 wt% of saccharide compound, instant invention). Harris et al. further teach in example D, col. 5, lines 30-40 the preparation of a quinapril composition with no saccharide in the formulation (claim 16, formulation does not contain a saccharide compound, instant invention).

Differences between the prior art and the claims (MPEP 2141.02)

Harris et al. do not teach an insoluble alkaline-earth metal salt of hydrogen phosphate. It is for this reason Daniel et al. is joined.

The teachings of Daniel et al. are incorporated herein by reference and are therefore applied in the instant rejection as discussed hereinabove. The suitable categories of drugs that can be combined in the embodiment of claim 12 of the instant invention are well known and well used in the art as categories that can be combined with ACE inhibitors, particularly quinapril, to provide an effective and efficacious anti-hypertensive agent with additive effects. Harris et al. and Daniel et al. teach the specific drugs of claim 12, including hydrochlorothiazide, dextromethorphan, and dextromethorphan hydrobromide (Harris et al., col. 2, lines 60-68 and col. 3, lines 1-10; Daniel et al., page 7, lines 11-26).

Finding of Obviousness/Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of the two cited references to produce a stable ACE inhibitor composition because Harris et al. teach it is within the skill of the art to make a stabilized ACE inhibitor composition comprising an ACE inhibitor, an alkali earth metal carbonate and 2% of a saccharide or no saccharide in the composition. Daniel et al. teach that dicalcium phosphate can be used as a hydrolysis minimizing agent, which performs the same function of retarding hydrolysis of an ACE inhibitor that is susceptible to hydrolysis. One skilled in the art at the time the invention was made would have been motivated to make the combination in order to receive the expected

benefit of a useful, stable formulation of an ACE inhibitor that will be preserved from cyclization and hydrolysis. Given the state of the art as evidenced by the teachings of the cited references, and absent any evidence to the contrary, there would have been a reasonable expectation of success in combining the teachings of the cited references to produce an effective, efficacious and stable ACE inhibitor formulation.

Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited reference.

Response to Arguments

Applicant's arguments filed December 8, 2008 have been fully considered but they are not persuasive. Applicant argues that Harris et al. and Daniel et al. combined do not suggest the instant invention that provides a formulation comprising a) an ACE inhibitor, b) an alkali or alkaline earth metal carbonate, c) an insoluble alkaline-earth metal salt of hydrogen phosphate, in a saccharide-free formulation. Applicant also argues that the examiner has not offered obviousness-rationale or motivation for why one skilled in the art would have added the dicalcium phosphate of Daniels et al. to the formulation of example D of Harris et al. which does not contain any saccharide compound.

In response to applicant's arguments, the Examiner respectfully disagrees with Applicant's traversal argument in reference to the motivation or suggestion to combine

the references. Daniel et al. teach that preferred hydrolysis-minimizing agents of the invention are saccharides, diuretics, and dicalcium phosphate, a calcium monohydrogen phosphate (page 9, lines 11-14). Daniel et al. teach that these agents can be used to retard hydrolysis in combination with an ACE inhibitor, which is susceptible to cyclization, hydrolysis, and/or discoloration (Daniel et al., page 3, lines 20-24). Therefore, it would have been prima facie obvious to substitute one hydrolysis-minimizing agent such as saccharides for another hydrolysis-minimizing agent such as dicalcium phosphate since the prior art establishes saccharide and dicalcium phosphate are functional equivalents. This gives the skilled artisan the motivation to combine the teachings of Harris et al. and Daniel et al. to formulate the claimed invention and also the motivation to add the dicalcium phosphate to the "inoperative composition" of Example D as taught by Harris et al. which would make the composition operable, diminishing the amount of hydrolysis.

Applicant also argues that lactose and dicalcium phosphate as taught by Daniel et al. are not functional equivalents. In response to Applicant's arguments, Daniel et al. specifically teach that saccharides, such as lactose, and dicalcium phosphate are preferred hydrolysis-minimizing agents. Daniel et al. teach that any of these agents can be used to retard hydrolysis in combination with an ACE inhibitor, which is susceptible to cyclization, hydrolysis and/or discoloration. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to use dicalcium

phosphate in the formulation because Daniel et al. teach that either lactose or dicalcium phosphate can be used to retard hydrolysis of ACE inhibitors.

Claims 1-12 and 15-16 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Harris et al. (US 4,743,450) in view of Daniel et al. (WO 99/62560) in further view of de Haan et al. (US 5,292,520).

Applicant's Invention

Applicant claims a pharmaceutical formulation of compound a) an ACE inhibitor, b) an alkali or alkaline earth metal carbonate, c) an insoluble alkaline-earth metal salt of hydrogen phosphate, and d) less than 5 wt% of a saccharide compound.

Determination of the scope of the content of the prior art (MPEP 2141.01)

The teachings of Harris et al. are incorporated herein by reference and are therefore applied in the instant rejection as discussed hereinabove. Harris et al. teach the quantity of the saccharide present will be from about 5% to about 90%, preferably about 10% to about 80% (col. 3, lines 56-58). Harris et al. further teach in example D, col. 5, lines 30-40 the preparation of a quinapril composition with no saccharide in the formulation.

Differences between the prior art and the claims (MPEP 2141.02)

Harris et al. do not teach an insoluble alkaline-earth metal salt of hydrogen phosphate. It is for this reason Daniel et al. and de Haan et al. are added as secondary references.

The teachings of Daniel et al. are incorporated herein by reference and are therefore applied in the instant rejection as discussed hereinabove. The suitable categories of drugs that can be combined in the embodiment of claim 12 of the instant invention are well known and well used in the art as categories that can be combined with ACE inhibitors, particularly quinapril, to provide an effective and efficacious anti-hypertensive agent with additive effects. Harris et al. and Daniel et al. teach the specific drugs of claim 12, including hydrochlorothiazide, dextromethorphan, and dextromethorphan hydrobromide (Harris et al., col. 2, lines 60-68 and col. 3, lines 1-10; Daniel et al., page 7, lines 11-26).

de Haan et al. teach a dry chemical composition containing a water soluble acid addition salt of a poorly soluble basic compound (e.g. a drug), an excipient selected from the group consisting of calcium hydrogen phosphate and a water soluble alkaline stabilizer (col. 2, lines 63-68). de Haan et al. further teach compounds useful to stabilize the tablets once made include sodium bicarbonate, anhydrous sodium carbonate, and sodium carbonate monohydrate (col. 4, lines 26-30). de Haan et al. further teach the preparation contains from 0.5 to 10% by weight of the stabilizer (col. 4, lines 43-45). de Haan et al. teach the amount of the excipient varies from about 30 to 80% by weight (col. 4, lines 21-25). de Haan et al. teach in example 1 the preparation of stabilized

tablets with a pharmaceutical compound, NaHCO3 (alkaline earth metal carbonate, instant invention) and calcium hydrogen phosphate dehydrate (insoluble alkaline-earth metal salt of hydrogen phosphate, instant invention). de Haan notes the compositions prepared by this formulation do not contain saccharide in the formulation, which unnecessarily adds to the costs of the formulation.

Finding of Obviousness/Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Harris et al., Daniel et al. and de Haan et al. and use an insoluble alkaline-earth metal salt of hydrogen phosphate in the composition. One skilled in the art would have been motivated to use an insoluble alkaline-earth metal salt of hydrogen phosphate as Daniel et al. teach that these agents can be used to retard hydrolysis in combination with an ACE inhibitor, which is susceptible to cyclization, hydrolysis, and/or discoloration. Therefore, it would have been prima facie obvious to substitute one hydrolysis-minimizing agent such as saccharides for another hydrolysis-minimizing agent such as dicalcium phosphate since the prior art establishes saccharide and dicalcium phosphate are functional equivalents. In addition, de Haan et al. teach that stabilized pharmaceutical tablets can be made with an excipient selected from the group consisting of calcium hydrogen phosphate and a water soluble alkaline stabilizer (col. 2, lines 63-68), with no saccharide in the composition. One skilled in the art at the time the invention was made would have been motivated to make the combination in order to receive the expected benefit of a useful, stable formulation of an

ACE inhibitor that will be preserved from cyclization and hydrolysis. Given the state of the art as evidenced by the teachings of the cited references, and absent any evidence to the contrary, there would have been a reasonable expectation of success in combining the teachings of the cited references to produce an effective, efficacious and stable ACE inhibitor formulation.

Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited reference.

Response to Arguments

Applicant's arguments filed December 8, 2008 have been fully considered but they are not persuasive. Applicant argues that Harris et al., Daniel et al., and de Haan et al. combined do not suggest the instant invention that provides a formulation comprising a) an ACE inhibitor, b) an alkali or alkaline earth metal carbonate, c) an insoluble alkaline-earth metal salt of hydrogen phosphate, in a saccharide-free formulation.

In response to applicant's arguments, the Examiner respectfully disagrees with Applicant's traversal argument in reference to the motivation or suggestion to combine the references. Daniel et al. teach that preferred hydrolysis-minimizing agents of the invention are saccharides, diuretics, and dicalcium phosphate, a calcium monohydrogen phosphate (page 9, lines 11-14). Daniel et al. teach that these agents can be used to retard hydrolysis in combination with an ACE inhibitor, which is susceptible to

cyclization, hydrolysis, and/or discoloration (Daniel et al., page 3, lines 20-24). Therefore, it would have been prima facie obvious to substitute one hydrolysis-minimizing agent such as saccharides for another hydrolysis-minimizing agent such as dicalcium phosphate since the prior art establishes saccharide and dicalcium phosphate are functional equivalents. This gives the skilled artisan the motivation to combine the teachings of Harris et al. and Daniel et al. to formulate the claimed invention and also the motivation to add the dicalcium phosphate to the "inoperative composition" of Example D as taught by Harris et al. which would make the composition operable, diminishing the amount of hydrolysis. de Haan et al. is added as a secondary reference to show that calcium hydrogen phosphates are functional equivalents to saccharides and are added to formulations to stabilize pharmaceutical formulations, particularly poorly soluble basic compound (e.g. a drug).

Applicant also argues that de Haan et al. disclose that lactose is listed as one of the excipients that can be used in the formulations. In response to Applicant's arguments, Applicant admits that lactose is a functional equivalent to the other excipients disclosed by de Haan et al., including calcium hydrogen phosphate and can be used in the formulations. The examples disclosed by de Haan et al. do not contain lactose in the formulations. In addition, de Haan notes the compositions prepared by this formulation do not contain saccharide in the formulation, which unnecessarily adds to the costs of the formulation. One skilled in the art would have been motivated to use a calcium hydrogen phosphate in the formulation because both Daniel et al. and de

Haan et al. teach that saccharides (lactose) are functional equivalent excipients that are used to stabilize pharmaceutical compositions, particularly ACE inhibitor formulations.

The claims remain rejected.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andriae M. Holt whose telephone number is (571)272-9328. The examiner can normally be reached on 7:00 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richter Johann can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Andriae M. Holt
Patent Examiner
Art Unit 1616

/John Pak/
Primary Examiner, Art Unit 1616